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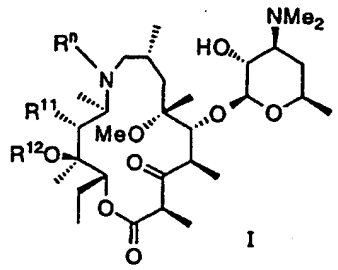
9a-Aza-3-ketolide antibiotics

(57) Compounds represented by formula I:



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and salts or hydrates thereof, wherein

R^{11} is OH or OCH_3,

R^{12} represents H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined below,

$(CH_2)_n$ is alkylene, wherein n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

R^n represents H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAR$ wherein $(CH_2)_n$ and Ar are as defined above, have antibiotic activity.

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TITLE OF THE INVENTION

9A-AZA-3-KETOLIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

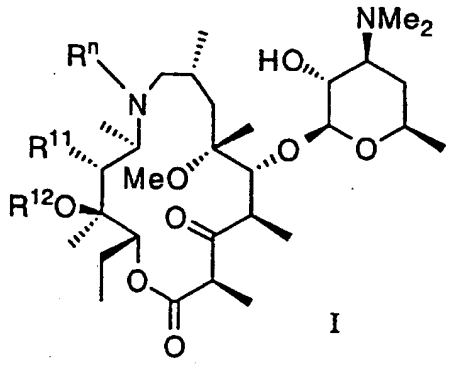
BACKGROUND OF THE INVENTION

The present invention relates to 9a-aza-3-ketolides, compositions containing such compounds and methods of use therefore. Azalides are structurally similar to erythromycin A, except for the presence of a ring nitrogen atom at the 9a-position. The compounds of the invention are further distinguished from erythromycins and erythromycin-like compounds in that the cladinose moiety has been cleaved from the molecule, and a carbonyl group is present at position 3. Additionally, the compounds of the present invention contain a 6-methoxy group.

The 9a-azalides of the present invention are potent antibiotics which are useful for the treatment of gram positive and gram negative organisms. As such the compounds find utility in human and veterinary medicine for the treatment of infections caused by susceptible organisms.

SUMMARY OF THE INVENTION

The present invention addresses a compound represented by formula I:



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or a salt or hydrate thereof wherein:

R^{11} is selected from the group consisting of: OH and OCH_3,

R^{12} represents a member selected from the group consisting of: H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined below,

$(CH_2)_n$ is alkylene, wherein n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

R^n represents H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined above.

Also included is a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

Also included is a method of treating a bacterial infection in a mammalian patient in need of such treatment which is comprised of administering to said patient a compound of formula I in an amount which is effective for treating a bacterial infection.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described in connection with the following definitions unless otherwise specified.

Alkyl refers to C1-6 straight or branched chain alkyl groups. The alkyl group can be uninterrupted or interrupted of O, $S(O)_y$ wherein y is 0, 1 or 2, N, NH, NCH_3 or C(O) as specified. When interrupted, a methylene spacer can be present which is adjacent to an interrupting moiety. Thus, this would include, for example, $-CH_2-O-$ and $-O-CH_2-$. When two or three of these interrupting groups is present, they may be separate or together. Me represents methyl.

Acyl refers to C_{1-5} alkyl-C(O)-.

When the group $-(CH_2)_nAr$ is present, the alkyl portion $-(CH_2)_n$ can be uninterrupted or interrupted as described above, with O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O). This includes groups where the interrupting atom is at either end of the chain. Thus, -C(O)-phenyl, -NH-phenyl, $-C(O)NH-(CH_2)_{1-10}$-phenyl, $-CH_2-O$-phenyl as well as like groups are included. Additionally, the alkylene portion can be substituted with 1-3 groups selected from R^a.

Each R^a is independently selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O).

Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 groups selected from R^a which is halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a substituent groups are attached to Ar, said substituents may be taken in combination with any intervening atoms to represent a 5-6 membered aromatic or non-aromatic ring, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, NH, NCH_3 or C(O) wherein y is as previously defined. Examples of Ar and Ar substituted with 1-3 R^a groups include phenyl, naphthyl, quinolinyl, isoquinolinyl, pyridyl, imidazolyl,

pyrrolyl, thiophenyl, benzothiazolyl, thiazolyl, furanyl, benzofuranyl, indolyl, fluorenonyl, dibenzofuranyl and naphthosultamyl.

Halo means Cl, F, Br or I.

A preferred aspect of the invention relates to compounds wherein R^{11} is OH. Within this subset, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds of formula I wherein R^{12} represents a member selected from the group consisting of: C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein

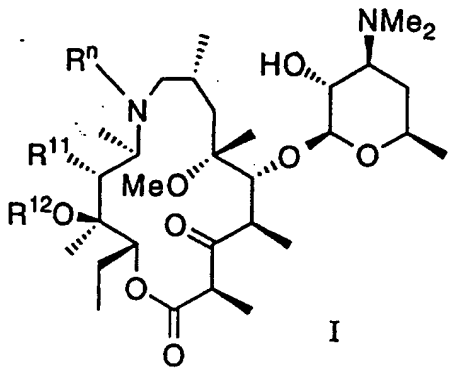
$(CH_2)_n$ is alkylene, n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O). Within this subset, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds of formula I wherein R^{12} represents H. Within this subset, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds of formula I wherein R^n represents H or C_{1-6} alkyl. Within this subset, all other variables are as orignally defined.

A preferred subset of compounds is defined in accordance with formula I:



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and includes salt and hydrates thereof wherein:

R^{11} is OH;

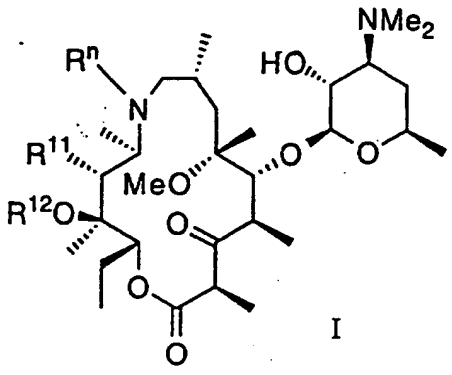
R^{12} represents a member selected from the group consisting of: C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$;

$(CH_2)_n$ is alkylene, wherein n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 R^a groups, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

R^n represents H or C_{1-6} alkyl.

Another preferred subset of compounds of the present invention is in accordance with formula I:



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and includes salt and hydrates thereof wherein:

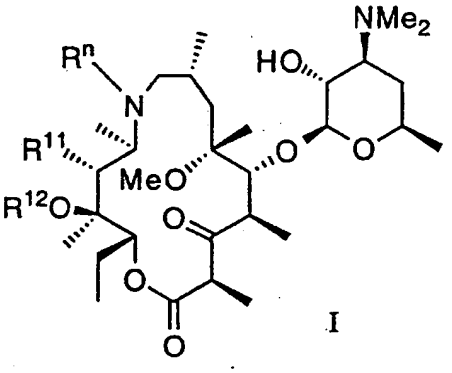
R^{11} is OH;

R^{12} represents hydrogen, and

R^{n} represents H or C_{1-6} alkyl.

Specific compounds which are included in the present invention are set forth below.

Representative Examples



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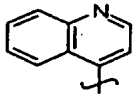
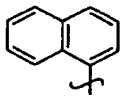
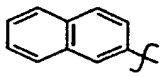
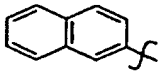
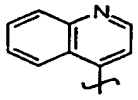
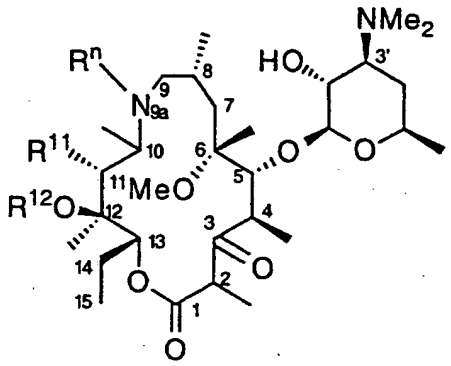
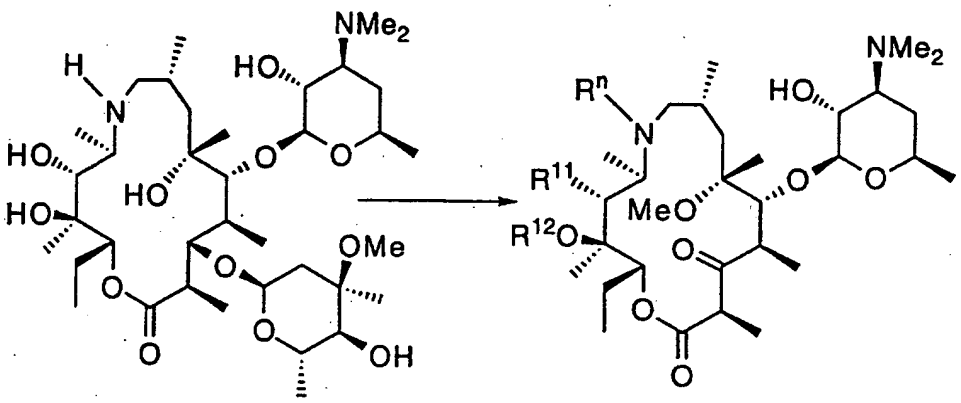
#	R^n	R^{11}	R^{12}	Ar
1	CH_3	OH	H	----
2	H	OH	H	----
3	CH_3	OCH_3	CH_3	----
4	CH_3	OH	$(CH_2)_4Ar$	
5	CH_3	OCH_3	$(CH_2)_4Ar$	
6	$(CH_2)_3Ar$	OH	H	
7	$(CH_2)SO_2Ar$	OH	H	
8	CH_3	OH	$CON(CH_2)_3Ar$	

Numbering of the 9a-aza-3-ketolides described herein is in accordance with the following scheme.



The compounds of the present invention may be prepared from 9a-aza-9-deoxo-9a-homo-erythromycin A by a variety of synthetic routes. The process is illustrated by the following generic scheme:

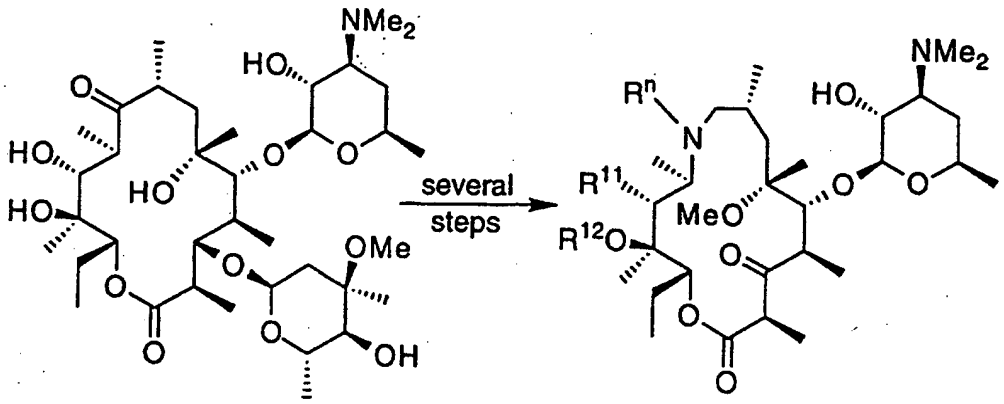
Scheme A



With reference to Scheme A, R^n, R^{11}, and R^{12}, are as defined with respect to the compounds of formula I.

Since 9a-aza-9-deoxo-9a-homo-erythromycin A is prepared from erythromycin, the compounds of the present invention are ultimately derived from erythromycin as shown in Scheme B. It will be further recognized that the the compounds of the present invention can be prepared from erythromycin without proceeding through the azalide intermediate shown above by simply altering the order of the steps described herein for the conversion of that intermediate to the compounds of the present invention and the steps required to introduce the 9a nitrogen.

Scheme B



At some point during the synthetic sequence, it is necessary to remove the cladinose attached at C-3 of the starting azalide. Depending on the exact nature of the final synthetic target, the cladinose removal may be best effected at either an early or late stage of the synthesis. This is generally accomplished by treating the macrolide with acid in either aqueous or alcoholic solution. Thus, a solution of the macrolide in an alcohol such as methanol, ethanol, or the like containing from 0.5 to 5% of a strong acid such as hydrochloric acid, sulfuric acid, or the like is stirred for 1 to 36 hours at a temperature ranging from 0°C to 30°C. Alternatively, a solution of the macrolide in a 0.1N to 1 N aqueous solution of a strong acid such as hydrochloric acid, sulfuric acid, or the like is stirred for 1 to 36 hours at a temperature ranging from about 0°C to 30°C. The reaction is worked up and the product macrolide isolated by first making the reaction mixture basic by adding an aqueous solution of a base such as sodium hydroxide, sodium bicarbonate, potassium carbonate and the like then extracting the macrolide product with a suitable organic solvent such as chloroform, ethyl acetate, and the like. If the reaction is run in an alcoholic solvent, the extraction procedure may be improved by first concentrating the reaction mixture under vacuum, preferably after addition of aqueous base to neutralize the acid. When working in the erythromycin series (ketone at C-9, free OH group at C-6), the C-9 ketone must be protected (e.g. as an oxime) before attempting to remove the cladinose under the

acidic conditions described above. In the azalide series (C-9 ketone removed with the addition of the 9a-nitrogen), no protection of a ketone at C-9 is necessary.

During alkylation of the C-6, 11, or 12 hydroxyl group, it is necessary to protect the nitrogen at C-3' in order to prevent quaternization of the nitrogen. This can be accomplished by protection of the desosamine as the 2',3'-bis-CBZ derivative by using standard macrolide chemistry techniques. Alternatively, the 3'-nitrogen atom can be protected as an arylsulfonamide by N-demethylation followed by sulfonylation with an appropriate sulfonyl halide or sulfonic anhydride. It is not generally necessary to protect the 9a-nitrogen during alkylation reactions. However, protection of the 9a-nitrogen may be useful since it can alter the order of reactivity of the various hydroxyl groups to alkylation.

Some reactions, including but not limited to alkylation reactions, may also necessitate protection of other hydroxyl groups. This may be accomplished by protection as a silyl ether, an ester, a mixed carbonate, or any of a variety of hydroxyl protecting groups well-known to those skilled in the art.

Alkylation of the C-11, or 12 hydroxyl group may be accomplished by treating a solution of a suitably protected macrolide in a suitable solvent such as dimethylformamide, tetrahydrofuran, and the like with a strong base such as sodium hydride, potassium hexamethyl-disilazide, and the like at a temperature ranging from -40°C to 25°C for 1 to 30 minutes then adding a suitable alkylating reagent such as an alkyl iodide, an alkyl bromide, an alkyl trifluoromethanesulfonate, and epoxide, and the like and stirring the resulting reaction mixture at a temperature ranging from -40°C to 45°C for 15 minutes to 4 hours (appropriate temperature and length of time depends on the exact nature of the alkylating reagent). Alkylation of the C-6 hydroxyl group is particularly difficult and, contrary to previous reports, requires the use of more efficient alkylating conditions than those described above.

Introduction of the 3-keto group is accomplished by oxidation of a suitably protected precursor with a hydroxyl group

at C-3 using one of the many methods for oxidation of secondary alcohols which are well-known to those skilled in the art. For example, a solution of the 3-hydroxy precursor compound in a suitable solvent such as dichloromethane, chloroform, dichloroethane and the like is treated with from 0.95 to 2 molar equivalents of an oxidation reagent such as pyridinium chlorochromate, pyridinium dichromate, Dess-Martin periodinane, chromic acid and the like for 0.1 to 24 hours at a temperature ranging from -40°C to 40°C. The reaction is worked up and the product macrolide isolated by simply filtering the reaction mixture through a piece of filter paper or through a plug of silica gel and evaporating the filtrate under vacuum. Alternatively, the reaction may be worked up by adding an aqueous solution of a base such as sodium hydroxide, sodium bicarbonate, potassium carbonate and the like then extracting the macrolide product with a suitable organic solvent such as chloroform, ethyl acetate, and the like. Evaporation of the organic extract under vacuum then affords the product. Alternatively, oxidation procedures commonly referred to by those skilled in the art as Moffat or Swern oxidations, which involve the use of activated DMSO reagents, may be employed for the oxidation of a 3-hyroxyl group to a 3-ketone. Oxidation using the Dess-Martin periodinane is preferred.

The synthesis of the target compound is completed by removing any protecting groups which are present in the penultimate intermediate using standard techniques which are well known to those skilled in the art. The deprotected final product is then purified, as necessary, using standard techniques such as silica gel chromatography, HPLC on silica gel or on reverse phase silica gel, and the like or by recrystallization.

The final product may be characterized structurally by standard techniques such as NMR, IR, MS and UV. For ease of handling, the final product, if not crystalline, may be lyophilized from, e.g., benzene, tert-butanol and the like, to afford an amorphous, easily handled solid.

The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The compounds of this invention may be used in a variety of pharmaceutical preparations. They may be employed in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically, orally and parenterally by injection.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral compositions

may utilize conventional formulating agents, and may include sustained release properties as well as rapid delivery forms. The preferred pharmaceutical composition is a table, capsule, suspension or solution, which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the particular compound selected, the virulence of the infection and other factors. Such matters are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts.

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from about 0.01% to as high as about 99% of active material, the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 2.5 g of the active ingredient; however, in general, it is preferable to employ a dosage amount in the range of from about 25 mg to 1000 mg.

The preferred method of administration is oral.

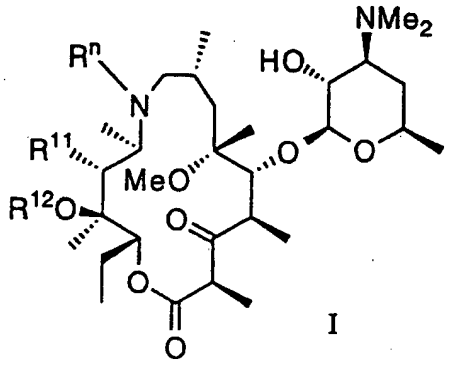
For adults, about 5-50 mg of the compound per kg of body weight given one to four times daily is preferred. The preferred dosage is 250 mg to 1000 mg of the compound given one to four times per day. More specifically, for mild infections a dose of about 250 mg two or three times daily is recommended.

For severe infections caused by organisms at the upper limits of sensitivity to the antibiotic, a dose of about 1000-2000 mg three to four times daily may be recommended.

For children, a dose of about 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg may be recommended.

WHAT IS CLAIMED IS:

1. A compound represented by formula I:



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or a salt or hydrate thereof wherein:

R^{11} is selected from the group consisting of: OH and OCH_3,

R^{12} represents a member selected from the group consisting of: H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined below,

$(CH_2)_n$ is alkylene, wherein n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

R^n represents H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined above.

2. A compound in accordance with claim 1 wherein R^{11} is OH.

3. A compound in accordance with claim 1 wherein R^{12} represents a member selected from the group consisting of: C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein

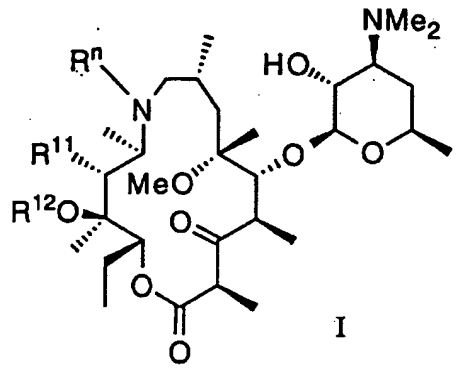
$(CH_2)_n$ is alkylene, n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O).

4. A compound in accordance with claim 1 wherein R^{12} represents H.

5. A compound in accordance with claim 1 wherein R^n represents H or C_{1-6} alkyl.

6. A compound in accordance with formula I:



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or a salt or hydrate thereof wherein:

R^{11} is OH;

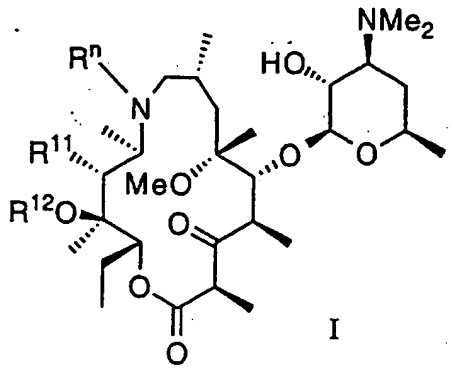
R^{12} represents a member selected from the group consisting of: C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$;

$(CH_2)_n$ is alkylene, wherein n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 R^a groups, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

R^n represents H or C_{1-6} alkyl.

7. A compound represented by formula I:



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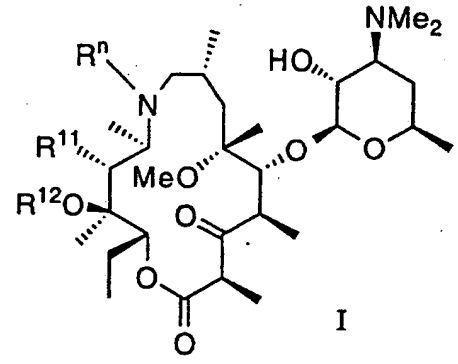
or a salt or hydrate thereof wherein:

R^{11} is OH;

R^{12} represents hydrogen, and

R^n represents H or C_{1-6} alkyl.

8. A compound in accordance with claim 1 falling within the following table:



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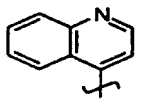
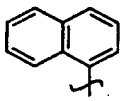
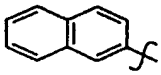
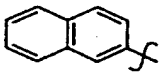
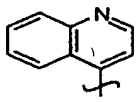
#	R^n	R^{11}	R^{12}	Ar
1	CH_3	OH	H	----
2	H	OH	H	----
3	CH_3	OCH_3	CH_3	----

4	CH_3	OH	$(CH_2)_4Ar$	
5	CH_3	OCH_3	$(CH_2)_4Ar$	
6	$(CH_2)_3Ar$	OH	H	
7	$(CH_2)SO_2Ar$	OH	H	
8	CH_3	OH	$CON(CH_2)_3Ar$	

9. A pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

10. A method of treating a bacterial infection in a mammalian patient in need of such treatment which is comprised of administering to said patient a compound of formula I in an amount which is effective for treating a bacterial infection.

The Patent Office

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Application No:	GB 9814269.8	**Examiner:**	Peter Davey
Claims searched:	1-10	**Date of search:**	9 September 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): C2C (CLK)

Int Cl (Ed.6): C07D 413/12

Other: Online: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	Chemical Abstracts 127:217667	1 at least
X	Chemical Abstracts 121:134695 and FR 2691464 A1 (ROUSSEL-UCLAF), see abstract	-

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.